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BIOLOGY OF TUMORS.

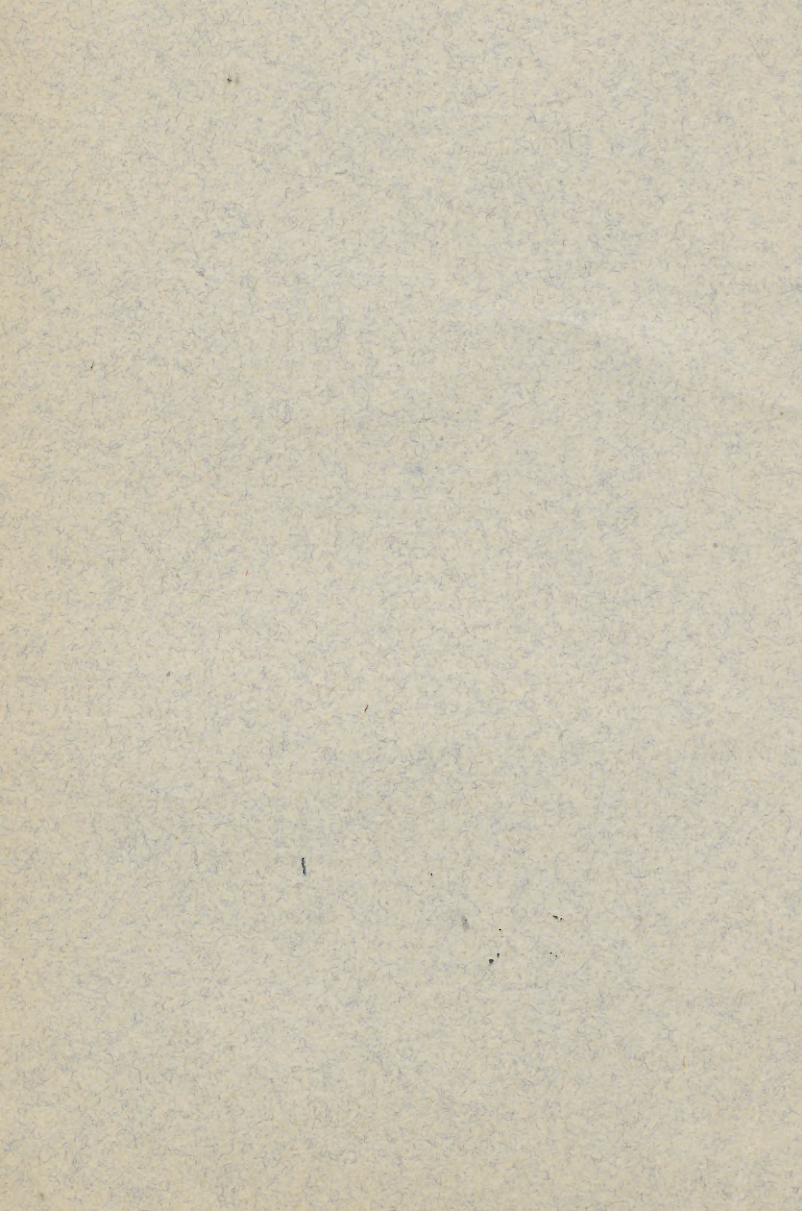
A LECTURE DELIVERED AT THE COLLEGE
OF PHYSICIANS AND SURGEONS,
CHICAGO, ILLINOIS,

By N. SENN, M.D., PH.D.,
Milwaukee, Wis.,

Professor of Principles and Practice of Surgery and of
Clinical Surgery in the College.



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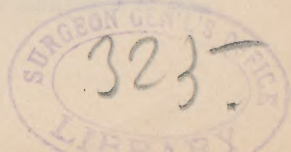
A LECTURE DELIVERED AT THE COLLEGE OF
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GENTLEMEN: In my last lecture I finished the subject of wounds, their treatment and their complications. I have so far described to you some of those infective diseases which by general consent and usage are assigned to the chair of surgery. The discussion of pathological conditions heretofore has been limited to a description of the production of new tissue as we observe it originating directly from the fixed tissue cell, or as a product of cell migration from the capillary blood-vessels. We have considered the subject of swellings in connection with inflammatory processes, and have been very careful not to call them tumors. I have endeavored to make it clear to you that a swelling of an inflammatory origin in every instance always differs from a tumor proper, from an anatomico-pathological standpoint.

Anatomically, an inflammatory swelling is one which occurs either as the result of migration of white corpuscles into the tissues, or as an increase of tissue by proliferation from preëxisting, mature, fixed tissue cells. Pathologically, an inflammatory swelling differs from a tumor, because the product of in-



flammation is either capable of transformation into tissue of a higher type or of retrograde transformation, disintegration, and complete removal by absorption—in other words, the product of inflammation gives rise to a swelling which shows no inherent tendency to remain as a permanent formation. A tumor, on the other hand, is an increase of volume from an atypical tissue proliferation from an embryonal matrix, and which manifests no disposition to disappear spontaneously. This is the sense in which Cohnheim uses the term. Luecke defines a tumor as an increase in volume by tissue proliferation without a corresponding increase in physiological function. We shall continue to use the term tumor strictly in accordance with the teachings of Cohnheim, and I will once more specify what we mean by “an atypical proliferation of tissue.” Virchow means by the term “tumor” a local growth of tissue from the fixed, mature tissue cells in accordance with his doctrine *omnis cellula e cellula*. Again, he subdivides tumors into such as have a homologous and heterologous origin, meaning by a homologous growth a tumor the tissue of which corresponds to the matrix in which it grows; as, for instance, a fibroma developing in fixed, mature connective tissue in contradistinction to a heterologous tumor, which implies the presence of tumor elements in a matrix which does not correspond with the histological structure and character of the preëxisting, fixed tissue cells in which it is found—as, for instance, the occurrence of an osteoma in a tissue normally devoid of an osseous matrix, as in connective tissue, muscles, lungs, ovary, testicle, and parotid gland.

Heterology in pathology has often been misunderstood, inasmuch as it has been applied as a term synonymous with malignancy. A heterologous growth is not necessarily a malignant tumor, and a malignant tumor, in the old sense of the word, is not always of a heterologous origin. A malignant tumor, in the sense in which Virchow used the term, is always a heterologous tumor, the tumor tissue occurring in a locality which does not correspond to the type of tissue found in the tumor. You will notice that we differ materially from Virchow's ideas as to the nature of a tumor ; we differ materially, inasmuch as we call every tumor " an atypical proliferation of tissue." It is difficult to conceive how mature connective or any other tissue, when normal in structure and function, should give rise to a circumscribed, permanent, local tissue growth. In opposition to these pathological views Cohnheim advanced the theory, which in many instances has been corroborated by facts, that every tumor, whenever and wherever it may occur, and whatever its character may be, is the product of tissue proliferation, not from mature, but from embryonal tissue. In this sense, then, every tumor is an atypical growth, as its component parts are not derived from preëxisting mature tissue, but from a congenital embryonal matrix. In a strict sense of the word a tumor matrix is always a heterologous formation ; as, for instance, a fibroma originating in a locality where we naturally expect to meet with fibrous or connective tissue ; the tumor does not spring from the mature, preëxisting tissue, but from an embedded matrix of embryonal tissue. We will take it for granted that every tumor matrix is composed of im-

mature or embryonal tissue which has remained in the embryonal state in a latent condition since embryonal life. You remember in my introductory lecture on tumors I gave you numerous instances which exemplify this pathological view concerning their primary origin. It is, of course, exceedingly difficult to prove the correctness of this supposition, as it is impossible in many instances to trace a tumor back to its original starting-point. So many instances have been cited which prove the embryonal origin of tumors that in the remaining cases we must recognize, at least for the present, a similar primary cause.

In order for you to more fully appreciate this part of our subject, I will take it for granted that here (drawing a reticulum of connective tissue on the blackboard) we have mature connective tissue. This aggregation of round, indifferent, embryonal cells represents the embryonal matrix, which has remained in a latent state for an indefinite period of time until, under the influence of some exciting cause or causes, a new impetus is imparted to it, which determines tissue proliferation, and the result is a circumscribed development of new connective tissue, which we call a tumor. Virchow taught that a fibroma originates from a proliferation of mature, fixed connective tissue. You must recognize the fact that the mature connective tissue takes no active part in the production of the tumor. The essential condition in every instance is the presence of a matrix of embryonal tissue. The last part of Luecke's definition of a tumor holds true inasmuch as in considering the biology of tumors you will notice, as a separate heading, that one of the characteristic fea-

tures of a tumor is the absence of function. For instance, in a myoma, no matter how large the tumor may be, and irrespective of its immediate surroundings, the muscular fibres have no physiological function, mainly from the absence of proper points of anatomical attachments. The same fact becomes apparent if we go still a step further and consider an adenoma, a proliferation from an embryonal matrix of adenomatous tissue, no matter what the size of the tumor may be, the conspicuous clinical feature remains—*absence of function*. So, in cases of carcinoma, whatever its component parts may be, whatever organ may be the seat of the neoplasm, we invariably recognize absence of function as one of its leading and characteristic features. As another typical illustration of this assertion I will call your attention to lymphoma, a hyperplasia of the elements of embryonal lymphoid cells embedded in one or more of the lymphatic glands—one of the most important of the hæmatogenetic organs. If you have occasion to study a case of multiple lymphomata, where a profuse cell-proliferation takes place from an embryonal matrix of lymphoid tissue, you will observe not only an absence of function, but an actual impairment of the process of hæmatogenesis. You will find in these cases, instead of an increase of the red corpuscles of the blood, almost without exception an anæmic condition of the patient. When we consider the essential anatomico-pathological conditions which must precede and accompany the formation of a tumor—in other words, the active cell-proliferation from a latent matrix of embryonal tissue—we must also have present another important factor, namely: adequate

quantitative and qualitative blood-supply. The importance of an adequate blood-supply in the growth of tumors is well illustrated by that form of growths that we so frequently meet with during the age of puberty—dermoid cysts. The growth of these cysts is determined by an increased physiological function of the entire organism, and more particularly of the skin and the organs of generation which take place during the age of puberty. The increased physiological blood-supply to special organs during this time of life explains the frequency with which we meet with dermoid cysts of the ovary, face, and neck in young adults.

To determine the growth of a tumor, it is not only necessary to have an adequate blood-supply, but the blood itself must contain the requisite nutritive and chemical ingredients which are necessary for the formation of tumor-tissue. In the development of an osteoma, it is not only necessary to have present an embryonal matrix of indifferent bone-cells, but the blood must bring to the part during the growth of the tumor the proper constituent elements (the earthy salts) which enter into the formation of bone. So, likewise, in a case of lipoma, it is not only essential to have present an adequate quantitative blood-supply, but the quality of the blood brought in contact with the tumor matrix must be such as to produce fat instead of connective tissue or bone. An increase of blood-supply favors tissue-growth, and in every instance we can refer it either to a physiological increase or antecedent pathological conditions. The increased physiological blood-supply is either general or local; the general increase giving rise to giant growth, which consists

in hyperproduction of normal histological elements throughout the entire body. Localized increase of physiological blood-supply leads to local hyperplasia, localized giant growth, which may implicate an entire organ or limb. Anything which in the organism will determine an increased physiological blood-supply to a preëxisting tumor matrix favors tumor-growth, an assertion so well illustrated in cases of tumors of the breast, commencing during pregnancy or lactation, at a time when the physiological increase of blood-supply exerts a potent influence in stimulating cell-proliferation from a latent matrix. So, in cases of uterine tumors, the periodical recurrences of congestion in the part affected, during menstruation, a condition is created which accelerates tissue-growth. Consequently myofibroma of this organ almost without exertion commence before the menopause, and their growth is frequently arrested with the cessation of menstruation. Surgeons have utilized this fact, and have adopted a therapeutic measure which aims at diminishing increased physiological blood-supply to this organ by suspending artificially this periodical function by the removal of the ovaries and Fallopian tubes in the treatment of myofibroma of the uterus. In speaking of a pathological increase of blood-supply in stimulating a latent tumor matrix into activity, I will first call your attention to traumatism as a cause of tumor-growth. You have already learned from my lectures on regeneration after wounds that every trauma is followed by an increased vascularity to the injured part. The direct effect of a trauma upon the terminal filaments of nerves produces a momentary reflex paresis, which causes an immediate capillary engorgement.

An increased physiological blood-supply to the injured part is also always produced by the collateral circulation which is initiated around the injured or divided vessels; so that traumatism may favor tumor-growth by furnishing at least one of the essential ætiological conditions—an adequate blood-supply. We have learned that hyperæmia constitutes one of the most characteristic features of inflammation, so that when a trauma is followed by this condition increased vascularization takes place. If this inflamed area should accidentally be at or near a matrix of embryonal tissue the increased afflux of blood secures the necessary physiological condition preceding active tissue-proliferation, and the latent cells assume an abnormal activity, the new product furnishing the building material for the tumor. If, as I have previously asserted, a tumor in every instance constitutes an integral part of the organism, there can be nothing mysterious or strange about its existence or location. The function of normal tissue implies the necessity of a regular, typical, physiological blood-supply. This is not the case in a tumor. We observe in every tumor an atypical vascularization, instead of a normal physiological blood-supply just sufficient to nourish the tissues, which alone is very suggestive in indicating the pathological structure and character of the new product.

A tumor may present an atypical vascularization, illustrated by an increased circulation, either arterial, venous, or capillary, as the case may be, according to its anatomical location, or the peculiarity of the structure of the new vessels in the tumor matrix or its immediate vicinity. The most striking examples of this form of atypical vascularization are furnished

by tumors which present pulsation as one of their most conspicuous clinical features. By a pulsating tumor we understand, clinically, a tumor where the pulsations are due to an atypical structure of the vessels in the tumor, in the majority of cases being directly caused by an increase in size or number of preëxisting vessels, and by the formation of new vessels. These new vessels are either entirely devoid of a proper vessel-wall, or, when this is present, it is defective, forming irregular cavities or spaces, into which the blood enters by some adjoining vessel and returns either in the same direction or empties into another vessel. This peculiar structure and arrangement of vessels in many sarcomatous tumors would explain the frequency with which pulsation can be elicited in examining these tumors, more especially if they have their starting-point in the interior of a bone. In making an examination of such tumors you will frequently find in the interior irregular blood-spaces, variable in size, which are entirely new structures, originating in the same way as the independent formation of new blood-vessels we described when speaking of the reparative process attending the healing of wounds, only that in this instance the vascular development is greatly in excess of the requirements of nutrition, and retards the growth and development of the newly formed cells. I will assume that this is a vein of considerable size (illustrating on the black-board), and that this is a blood-space formed by canalization and endo-vascular production of blood corpuscles ; by gradual growth and dilatation this cavity is brought in contact with the vein-wall, and by a process of pressure atrophy a communication is es-

tablished between the preëxisting vein and the new blood-channel, which of course determines atypical vascularization in excess of the requirements of tumor growth, and imparts to the tumor important clinical and pathological features. The blood entering such spaces from adjacent vessels, and not meeting with normal resistance on account of a defective vascular wall, produces pulsations, and in many instances a marked bruit can be heard on auscultation, caused by the irregular distribution of the blood in the atypical vessels. These are the cases described by the older surgeons and pathologists as "bone aneurisms." A simple hemorrhagic cyst resembles one of these new blood-spaces, with or without a communication with adjacent vessels. Imagine with me, for a moment, the production of one of these blood spaces, and the formation of a communication between it and one or more of the adjacent vessels, an accident which would necessarily suddenly increase the intra-vascular pressure in the new channel, and thus modify the vascular supply ; it will furnish you an admirable example of what we understand by the term "atypical vascularization." The new vessels in a tumor, when imperfect in structure and largely dilated, often become the seat of mural thrombosis, the irregularity of surface presenting projecting points, upon which, by conglutination, the third corpuscles of the blood become arrested, and form a white thrombus which, when it completely obstructs the vessel, gives rise to coagulation necrosis in the impeded blood current on the distal side and the formation of a red thrombus. Another form of thrombosis and obliteration of the lumen of a vessel, as after ligature of a vessel, is met with as the result

of perforation of the vessel-wall by a neoplasm. This constitutes one of the most interesting conditions in the morbid anatomy of tumors. This pathological process is most frequently—I might say, almost exclusively—met with in malignant tumors. If, for example, this vein, a vessel of considerable size (illustrating on the blackboard), is surrounded by tumor tissue, which attacks the vein-wall directly, destroying preëxisting structures by infiltration, retrograde metamorphosis, and pressure atrophy, until by perforation the tumor projects into the vein, forming a neoplastic thrombus composed of tumor tissue, when the axial blood-current comes in contact with abnormal tissue, that tissue being devoid of the physiological properties required for a normal circulation, the thrombus increases in size by conglutination of the third corpuscle upon the most prominent projecting point, the thrombus serving as a foreign body in the vessel, mural stasis of the white corpuscles also takes place, the conglutinated and aggregated corpuscular elements of the blood furnishing a most favorable soil for further cell-proliferation from the intra-vascular neoplasm, which necessarily soon terminates in complete obliteration and obstruction of the affected vessel. This neoplastic thrombus always manifests a tendency to increase in size by infiltration of the blood coagulum with tumor cells, and when loose fragments become detached they are carried along with the blood-current, which arriving at a point too narrow for their passage become arrested, and give rise to embolic metastasis. In some cases embolism takes place by the projection of the proximal end of the thrombus into the lumen of a larger

vessel, small fragments, becoming detached, are washed away by the blood-current ; embolism in such cases establishes independent centres of growth wherever deposits take place, the products of tissue proliferation at the distant points corresponding in every respect with that of the primary matrix. As in cases of septicæmia and pyæmia, the emboli produce at distant points the same characteristic tissue changes that are typical of the local thrombus, so in cases of thrombosis and embolism in malignant growths the distant secondary tumor produced by an embolus from a neoplastic thrombus corresponds in structure and type with the primary formation. Thrombosis and embolism in such instances effect a transplantation, as it were, of the local product to some distant part through the veins as mediums of communication, the secondary tumors being the direct offsprings from the maternal or primary growth. Fragments of the tumor having been swept away, each retaining its vitality and identity, which, meeting with favorable conditions for cell-proliferation at the seat of localization, produce in distant organs the same neoplastic deposit which we observe at the primary seat of tumor formation. This is what we understand by thrombosis and embolism as applied to malignant growths.

I have described the process of tumor growth as taking place from an embryonal matrix, giving rise to new tissue, representing, however, the indifferent cells of the matrix, differentiation taking place during the growth and development of the tumor, so that the mature tumor tissue indicates with unfailing certainty the embryonal origin of the matrix. We shall now take up a few of the retrograde transforma-

tions which we meet with in cases of tumors, both benign and malignant.

In the beginning of the lecture I placed special emphasis upon the permanence of tumor tissue as compared with inflammatory swellings. Circumscribed, slow growth and great durability of tissue characterize benign growths; rapid, progressive growth and early destructive changes are the most conspicuous clinical features of malignant tumors. It is true that Virchow and Cruveilhier have described certain favorable retrograde tissue changes, which indicate that even tumors of the most malignant character occasionally manifest a tendency to spontaneous arrest of growth, always an indication that active proliferation has ceased, and preëxisting cells are undergoing retrograde metamorphosis. Bichât has described a form of atrophic cancer, which is occasionally met with in the breast, and is noted by its slow extension and numerous depressions, which denote absorption of tumor tissue, arrest of growth, and disappearance of tissue by retrograde transformation and absorption. The first changes indicating atrophy are generally observed in the oldest portions of the tumor, where the vascular supply and nutrition have become defective. Although the process has become stationary at certain points, even in this, the most benign form of true carcinoma, extension goes on slowly, but relentlessly, in a peripheral direction. Of central disintegration, the most frequent form is fatty degeneration, a retrograde metamorphosis which indicates to the pathologist a local area of anæmia, arising from imperfect vascularization of the neoplastic deposit, which again can be referred to defective vessel growth

or destruction of preëxisting vessels from compression or thrombosis by the neoplasm. As we have described tyrosis in tubercular deposits as one of the consequences of local anæmia, so in cases of malignant growths the vascularization does not always keep pace with tissue proliferation, and the result is a localized anæmia in the oldest portions of the tumor, an inadequate nutrition of the tumor elements, and, as a necessary consequence, we observe malnutrition, fatty infiltration and degeneration, disintegration and absorption of the tumor elements.

Calcification of a tumor is another retrograde change following fatty degeneration, which positively and permanently arrests tumor growth wherever this condition is established.

Another effect on part of the tumor cells results from their action upon the adjacent connective tissue, as they act like foreign bodies, which cause a connective-tissue proliferation, inducing a condition of sclerosis by contraction of the connective-tissue proliferation between the tumor elements, which constricts the vessels, causing a local anæmia, which not only produces compression of vessels and local anæmia, but causes at the same time strangulation of the tumor elements and pressure atrophy ; consequently sclerosis very frequently is the direct cause of retrograde metamorphosis, and is looked upon as a favorable change in the clinical course of a malignant tumor. As a rule, to which there are few exceptions, it may be stated that *the firmer the tumor, the less its malignancy ; the softer the tumor, the greater its malignancy*. Fibrillation of a sarcoma resembles sclerosis, and acts in a similar manner in retarding tumor

growth by compression of the vessels and strangulation of the cells, conditions which produce retrograde nutritive changes and retard peripheral growth. Any tissue changes, either within or in close proximity to a tumor, which diminish the vascular supply, are conditions which retard its growth and extension. Tyrosis occurring in granulation tissue we have described as a secondary pathological condition, indicative of the presence of the specific cause of tuberculosis, "the bacillus of tuberculosis." We have alluded to local anæmia as a cause of cheesy degeneration, but it remains an open question whether this change can take place independently of the bacillus, so that when this form of metamorphosis is found in a tumor, it is well to inquire into the presence or absence of the specific influence which clinically determines tyrosis. A tumor may become the seat of infection with the bacillus of tuberculosis, and the presence of this specific cause will determine the character of the retrograde changes. It is only reasonable to assume that the atypical vascularization of tumors furnishes a condition favorable to localization of floating germs, and consequently constitutes one of the causes of auto-infection. One of the most frequent forms of retrograde transformation in tumors of the connective-tissue and epithelial type is colloid degeneration, a transformation of the tumor elements into an amorphous albuminoid substance. As this change infers the substitution of the histological elements of the tumor by a structureless substance, its existence can be demonstrated by the presence of cavities or cysts, containing a translucent amorphous material. Whenever an area of absolute local anæ-

mia occurs in a tumor as a result of defective primary vessel growth, or as a secondary pathological condition, within or around the tumor, or in consequence of surgical interference, all nutritive changes cease, and gangrene or sloughing occurs, the same as I have described in speaking of gangrene as following acute inflammation. It is one of the ways in which, occasionally, a spontaneous cure is accomplished when the tumor is non-malignant. An effort in the same direction is often observed in cases of rapidly growing malignant growths where vascularization is inadequate to supply the tissue so rapidly produced by the local process, hence sloughing takes place in portions of the tumor where the local blood-supply has been sufficiently impaired to interfere with the proper nutrition of the tissues. While such an occurrence often destroys a malignant tumor, a recurrence at the site of cicatrization is the rule. A more circumscribed form of rapid disintegration is frequently met with upon the surface of rapidly growing tumors, and is again referable to imperfect circulation, caused by pressure from within outward. Molecular death or necrobiosis leads to ulceration at a point where the tumor has encroached upon the cutaneous covering. The infiltration of the subcutaneous cellular tissue by the neoplasm or inflammatory products diminishes the vascular supply to the skin, giving rise to superficial ulceration. Unless the necessary antiseptic precautions are observed when this complication arises, the most serious consequences may follow, as infection may lead to putrefaction of the surface secretions, infective inflammation, septicæmia, thrombophlebitis, and pyæmia. On this account it is always

advisable to anticipate a breach of continuity by resorting to timely antiseptic precautions.

As we have characterized permanence as one of the most important and characteristic clinical features of a true tumor, I will again refer to this subject and call your attention to enlargements of the thyroid gland as affording the best illustrations of the difference between a tumor and a swelling. One kind of enlargement which has been and still is erroneously designated as a tumor is the *struma miasmatica*. According to our views a struma due to miasmatic causes is not a tumor, because the early use of proper therapeutical agents, such as the administration of iodine, by neutralizing the primary cause, succeeds in effecting a cure. Under the influence of iodine fatty degeneration, disintegration, and absorption of the new tissue are effected and a restitution *ad integrum* takes place. The swelling or pseudo-tumor disappears, because the remedy administered has succeeded in removing the primary cause in contradistinction to the more permanent and true tumors of the thyroid gland springing from a remnant of embryonal tissues which constitutes the only and sole matrix of any tumor, and in such cases medication is worse than useless. A hyperplasia of tissue due to an infective cause is amenable to absorption or removal on neutralization of the primary cause, but no such termination can be expected in case of a tumor, whatever its structure and character may be.

Benign tumors are characterized by their slow growth and more typical vascularization, and are thus less liable to retrograde metamorphosis than malignant tumors. A benign tumor often comes to a

standstill—limitation of growth is one of its benign features, but under no circumstances does it disappear spontaneously, unless secondary pathological conditions are induced artificially or spontaneously, which destroy the entire matrix of the tumor. In such cases the destructive process may be regarded as a substitute for the surgeon's knife. In malignant tumors the degenerative and inflammatory changes only partially fulfil the indications, and the tumor continues to grow from independent centres wherever complete destruction has not been accomplished. Another important reason for the obstinacy of a malignant tumor to yield to local destructive changes we find in the inherent tendency of such a tumor to invade adjacent vessels, lymphatics, and veins, which contribute largely to the early local extension and general dissemination. Any tumor which during its clinical history is reproduced in a distant part or organ is a suspicious one, and in the majority of cases it is safe to pronounce it malignant. Primary multiplicity speaks in favor of non-malignancy; on the other hand, multiplicity occurring in the course of lymphatic vessels and veins from a single primary tumor is almost an infallible sign of malignancy. It is important to refer to the manner and direction of growth of a tumor, so as to obtain some information concerning its clinical history with special reference to decide the question of malignancy. A benign tumor is characterized by local growth, the increase in volume taking place in a central direction; consequently the margins of the tumor are well defined and its attachments to adjacent parts loose. In this connection permit me to call your attention to Virchow's

description of the manner of growth of benign tumors. In accordance with his doctrine that tumors are formed by transformation of mature preëxisting tissue, he asserts that even in benign tumors the growth is usually in a peripheral direction—in other words, he assumes additional foci of growth in the immediate vicinity of the primary growth and the formation of the tumor by confluence of separate centres of tissue-growth. For instance, in the development of a fibroma from connective tissue, he explains the increase in size by assuming that the immediate vicinity of the nucleus of the tumor shows evidences of the formation of local foci for additional centres of growth, which, by confluence amongst themselves and with the central nucleus, give rise to peripheral extension. Remember that Virchow believed at that time that a fibrous tumor always developed from preëxisting, mature connective tissue, and that the immediate cause of cell-proliferation in the peripheral zone of connective tissue he referred to the presence of a fluid or *seminium* emanating from the central focus, which was supposed to exert an infective influence upon the surrounding tissue. More accurate observations, and more careful microscopical examinations, however, have demonstrated the fact, which is in accord with our own views, that in benign growths originating from a matrix of embryonal tissue, the tissue-growth is limited to the preëxisting embryonal cells and the adjacent mature tissue takes no active part in the growth of the tumor. The adjacent normal tissue occupies an entirely passive rôle, and is subject to pathological changes only in so far as it is affected by pressure or accidental pathological changes occurring

in the immediate vicinity of the tumor. Mature tissue never serves as the starting-point of a tumor, and takes no active part in its future growth and development. If a benign tumor is the product of cell-proliferation from a circumscribed primary matrix of embryonal tissue, its increase in volume takes place in the direction which offers the least resistance. Peripheral growth by means of independent centres of growth is one of the most significant features of malignant tumors. The primary starting-point of a carcinoma or sarcoma is again a matrix of embryonal tissue, but peripheral extension takes place by infiltration of the adjacent connective-tissue spaces with cells from the central nucleus, which establish in all directions independent centres of growth. The peripheral growth of a malignant tumor is not due to any active participation of preëxisting, mature tissue; the rapid growth and speedy invasion of adjacent parts are entirely due to the transplantation of tumor elements into new fields where they produce tissue which resembles the primary tumor. Peripheral growth by infiltration must be accepted as one of the most important and earliest diagnostic features between a malignant and benign tumor. This zone of infiltration around a malignant tumor under the microscope so closely resembles the histological appearances during the early stage of inflammation that Waldeyer has applied to it the designation "inflammatory zone." The appearance of inflammation imparted to the microscopical picture is, however, not due to inflammation, but is produced by infiltration of new tissue elements from the central tumor. The only evidence of inflammation that presents itself is the presence of small cells

in the immediate vicinity of the tumor, which are not the products of inflammation, white corpuscles, or granulation tissue, but new tumor cells, which have wandered from the primary matrix of a sarcoma or carcinoma into the surrounding connective-tissue spaces. Remember that, clinically, the great anatomical distinction between a benign and malignant tumor is the manner of local growth, the former a movable, circumscribed tumor with central growth, the latter a peripheral growth giving rise to rapid infiltration of adjacent tissue, hence early fixation of the tumor without a well-defined boundary-line between healthy and morbid tissues.

In every instance, uncomplicated by inflammatory changes, where a tumor is intimately connected with the adjacent surrounding tissue, as evidenced by fixation and anatomically by the absence of a proper boundary-line between healthy and morbid tissue, you are safe in pronouncing the tumor malignant, and may adopt a treatment in consonance with such view. On the other hand, when a tumor has increased in size very slowly, and increase in volume takes place in a central direction, and where the absence of the so-called inflammatory zone can be ascertained by the presence of a well-defined boundary-line between the tumor and adjacent tissues, as determined by the mobility of the tumor and absence of attachments and metastasis, you may in the majority of cases predict with safety a benign course of the tumor. The older surgeons believed that malignancy was due to intrinsic qualities of the tumor elements themselves. I shall attempt to show you that malignancy, in the true pathological sense of the word, is attributable more

to the surrounding tissues than to the tumor elements themselves. It is true that Friedländer has shown that embryonal epithelial cells, by virtue of their amoeboid movements, can penetrate a subjacent inflamed surface. It has been shown that cancer-cells possess the same amoeboid movements which might be a potent factor in the process of infiltration. An examination of an isolated cell under the microscope, as to shape and structure, may enable the observer to trace it back to its proper embryonal source, but can afford no positive information as to its pathological significance. Even expert microscopists are often unable to distinguish granulation tissue from sarcomatous tissue, or to recognize a difference between epithelial cells from an epithelioma and a papilloma. A reliable anatomical diagnosis is based more upon an examination of the cells *in loco*, and their relations to the surrounding stroma, than a study of the morphology of isolated cells. The location of a cell more frequently decides its character than its morphology. The cell may be normal in structure and appearance, but, when its surroundings are abnormal, it belongs to an atypical structure in the sense in which Waldeyer uses this expression. How shall we explain that the same cell under certain conditions shows no tendency to local invasion and to distant metastasis, while in another locality, with different surroundings, it manifests evidences of the greatest malignancy? The results obtained by experimental research will furnish most important information. Numerous experiments of tumor implantations have failed. What has been the result of transplantation of tumor-tissue in animals? A short

period of tissue-proliferation, arrest of growth, to be followed, almost without exception, by retrograde metamorphosis and complete disappearance of the transplanted tissue by absorption. The results have been about the same whether the tissue was taken from a benign or malignant tumor. I have myself made experiments on man in performing partial operations in hopeless cases of carcinoma of auto-transplantation, but the results were always negative. These experiments teach a most important lesson. They show conclusively that the tissues around the tumor matrix exert a most important influence in the causation and retardation of tumor-growth. One of the most frequent causes of retardation of tumor-growth is a diminution of the local blood-supply, due either to the anatomical peculiarities of the part affected, or to secondary pathological conditions in the immediate vicinity of the primary matrix. The fact remains, that atypical vascularization, in the direction of producing local anæmia, retards tumor-growth, and yet all efforts aimed at starvation of malignant tumors, by cutting off the blood-supply, have failed in producing permanent results. While such measures may retard, they cannot be relied upon in arresting tumor-growth.

Another condition which has reference to vascularization of a tumor is age. It is a well-known fact that in young adults a tumor grows more rapidly than in the aged, on account of the activity of the general circulation, and, in certain localities, by an increased physiological blood-supply to the part.

I have yet to speak of the important part exercised by the adjacent tissues in favoring tumor-growth. I

refer to a diminution of the physiological resistance, whatever that may be, as demonstrated by the transplantation experiments of Cohnheim and Maas. These experimenters introduced into the jugular vein of animals small pieces of periosteum, with the expectation that they would become arrested in the smaller branches of the pulmonary artery as emboli. The animals were killed in a few weeks or months later, and the specimens examined to ascertain the time and extent of tissue-growth from the periosteal grafts. The results were uniform. The periosteum retained its osteogenetic properties and produced bone, but the new product was always limited in size to the lumen of the vessel in which the periosteal embolus had become impacted. When this size was reached further growth became arrested, and the new tissue, in the course of time, underwent complete removal by absorption. It is evident that the intrinsic force in the adjacent living tissue exerted a positive, undeniable influence in resisting tissue-proliferation. The same investigators have also shown that transplantation of embryonal tissue is more successful than when they used mature tissue. In the growth of an osteoma, tissue-proliferation takes place from an embryonal matrix, and we must assume that, in the immediate vicinity of the matrix, a diminution of the physiological resistance of the tissues had taken place. In the transplantations of malignant tissue, which have almost without exception been followed by negative results, we can only explain the failures by taking it for granted that the adjacent connective tissue presented an adequate physiological resistance, which prevented infiltration

of the transplanted cells, and that the graft acted like a foreign body, a process of healthy, active granulation around the new tissue in the course of time removing completely the malignant graft. The physiological resistance in the adjacent tissues permits grafts from benign tumors only to grow to certain dimensions, and eventually causes their removal by absorption, while it offers an effective barrier to infiltration by cells from grafts taken from malignant tumors.

From what I have said you must have satisfied yourselves that there are two essential conditions which must be present wherever a tumor grows, viz. : (1) an embryonal matrix, and (2) a diminution of the physiological resistance in the tissues in the immediate vicinity of the matrix. The absence of the former precludes entirely the possibility of the formation of a tumor, and only the presence of the latter enables the matrix to proliferate tumor-tissue. Future research must determine what conditions produce diminution of physiological resistance. We have reason to believe that this inherent property is often defective as an essential condition, and that it can be artificially produced by prolonged irritation and inflammation. That the chemico-vital changes which take place in inflamed tissue diminish physiological resistance has been unmistakably demonstrated by the experiments of Friedländer, to which I have already called your attention. Anything which produces inflammation in the immediate vicinity of a tumor increases tumor-growth, by reducing the physiological resistance and by increasing the vascular supply. You will have abundant opportunities to observe the rapid exten-

sion of cancer, after the vain attempts of quacks to cure this disease by the application of caustics. You will also become aware by future observation that all irritant applications to a malignant tumor invariably aggravate the disease. You will become satisfied that in all cases where a tumor has remained in a latent condition for an indefinite period of time, that all inefficient attempts calculated to effect its destruction will aggravate the condition still further by diminishing the physiological resistance of the adjacent tissues, which have become the seat of prolonged irritation or inflammation.

Another condition which probably favors tumor-growth indirectly by diminishing physiological resistance is traumatism. While many surgeons are willing to attribute almost every tumor to a traumatic origin, I shall assign to this cause a more indirect and subordinate position. It has been shown by Blum, who collected 100 cases of tumors, both malignant and benign, with especial reference to prove their traumatic origin, that in only twelve to fourteen per cent. could the patient or surgeon trace the tumor to a trauma. Influenced by a preconceived idea, it is not difficult to trace many of the local affections to a traumatic origin. How long have we been in the habit of looking upon traumatism as one of the most frequent causes of suppurative inflammation? Recent research has demonstrated that no degree of traumatism is followed by suppuration, unless it is followed by infection with the essential cause—the pus-microbes. Trauma in exceptional cases may, and probably does, act as an exciting cause in the growth of a tumor by producing inflammation, the condition I

have just described as one of the indirect causes of tumor-growth. Traumatic inflammation in the immediate vicinity of a latent tumor matrix is attended by a diminution of physiological resistance, which removes the barrier to tissue proliferation from the heretofore latent matrix, and in this capacity it deserves mention as one of the etiological conditions. When a trauma is inflicted upon a part, the seat of a matrix, it may be the indirect cause of the subsequent growth of a tumor; but when no such matrix is present, it can be followed by an inflammatory swelling, but never by a true tumor. But there are a great many cases where we are unable to trace any particular local exciting cause or causes which might explain the growth of a tumor, and we are forced to continue the investigation as to its causes. This brings us to the old and still obscure subject—the heredity of tumors.

A large class of pathologists have attributed the origin and development of tumors almost exclusively to hereditary causes. It is true, that in many instances it has been possible to trace a hereditary disposition through several generations, in this respect showing a great resemblance to congenital malformations. With our theory concerning the essential cause, it is not difficult to explain the heredity of tumors. During embryonal life a group of indifferent cells fail to undergo further development, and remain unutilized in the process of growth and regeneration of the tissues, to serve at some future time as a matrix for tumor-growth. In this sense all tumors are congenital. It is more than probable that many persons hold in their bodies an embryonal matrix, but on

account of the absence of the necessary exciting causes they never suffer from a tumor. The matrix remains latent throughout the entire lifetime of the individual. What renders a tumor hereditary is not only a congenital matrix, but a matrix with an inherited defective physiological resistance of the adjacent tissues. When both of these factors are congenital, the tumor can be called hereditary, in every sense of the word. It is very possible that future observation and research will explain in a satisfactory manner in what way the same matrix can produce a benign or malignant tumor, by being able to show that the type of the tumor depends upon the extent and character of that negative determining influence which we have termed reduction of physiological resistance, as that reduction may enable the tumor matrix to produce a local benign tumor, while complete suspension may furnish a condition in the immediate vicinity of the tumor, which indirectly determines cell infiltration, the characteristic feature of malignant growths.

On a previous occasion you were informed what we understand by the word "infection" with pathogenic germs; this term is also used in describing the local and general dissemination of malignant tumors. But in this connection we assign to the word a different meaning. Although we observe at the bedside a certain analogy and close resemblance between malignant tumors and infective inflammatory processes in the manner in which they invade adjacent and distant organs, no one so far has demonstrated the presence of germs in malignant tumors to the satisfaction of surgeons and pathologists, much less their etio-

logical relationship. While every surgeon has been forcibly impressed with the analogy of the manner of local extension and dissemination of malignant growths and tuberculosis, the most careful investigators have failed to establish a microbic origin for the former, while the latter furnishes the most typical instance of diseases due to a bacterial cause. To prove the microbic origin of a disease you must first be able to demonstrate the uniform presence of the same germ; the germ must be isolated and reproduced upon an artificial sterilized culture substance, and the new product when introduced into the tissues of a living animal must produce identical pathological conditions. All of these things must be accomplished before we can apply the designation "infective" (in the usual sense of the word) to malignant tumors. Infection in the sense in which we use it in connection with malignant growths resembles infection with germs, in so far that the essential primary cause is reproduced in the body and reaches adjacent tissues and distant organs through preëxisting spaces and channels from a central starting-point. The pathological conditions are, however, widely at variance. The germs act upon preëxisting tissue as irritants, producing inflammatory swellings with varying products, in accordance with the nature of the primary cause. Infection from a tumor implies auto-transplantation of tissue elements into the adjacent tissues, or through the medium of the lymphatics or blood-vessels in some distant organ, whereby reproduction of new tissue takes place which resembles the primary growth, not from preëxisting tissue, but from the transplanted cells. Tumor transplantation experi-

ments have uniformly proved unsuccessful, because the grafts have been brought in contact with tissues endowed with a normal physiological resistance. Infection with cells, like germ infection, wherever it occurs, establishes an independent centre of growth, the products of which resemble the primary depot. In each instance we must assume at the points of localization conditions favorable to cell growth or germ reproduction; for the former to take place we are forced to recognize as an essential condition reduction or complete suspension of the physiological resistance in the tissues brought in contact with the matrix. Local infection around a malignant tumor presupposes a zone of infiltration with young tumor-cells which takes place early or late, remains circumscribed, or becomes diffuse according to the size and form of the cells or the anatomical structure of the adjacent tissues. It is the existence of this zone of infiltration which leads so frequently to recidivation after extirpation of a malignant tumor. The surgeon has removed a malignant tumor, as he has reason to believe, very thoroughly, because he has made his incisions far beyond the macroscopical boundary-line, and yet after a few weeks or months he observes a return of the disease at the site of operation. It is plain that the local return was due to an imperfect operation; while care was exercised to make the incisions through healthy tissue the infiltration zone had not been thoroughly removed, and the embryonal cells in apparently healthy tissue reproduced the tumor. The uniform presence of such a zone around all malignant tumors should dictate to every prudent surgeon the practical importance of removing, not only the visible

tumor, but wherever it is practicable and consistent with the anatomy of the part to go far beyond its limits, so as to remove completely the infected tissue, holding in suspension the malignant embryonal elements which have wandered from the primary depot into adjacent connective-tissue spaces. It is also advisable to so direct the incisions as to include as much of the lymphatic glands and vessels as may appear compatible with the anatomical region, so as to guard against metastatic recidivation. The frequency with which imperfect operations are done has induced Nussbaum to express the opinion that, as a rule, surgeons operate badly for cancer. Many operations for malignant tumors are formidable ones, as they require careful anatomical dissections in close proximity to important structures. The prime indication that presents itself is the removal of all infected structures without regard to the less important matter of the subsequent closure of the wound. No more striking illustration can be cited than the improved results that have been obtained after excision of cancer of the breast, since we have learned that success depends upon a typical clearing out of the axillary space to the upper border of the first rib, combined with a thorough removal of the tumor and the infected tissues in its vicinity. Another good reason against carrying an incision through affected tissue is the danger arising from the liberation of neoplastic cells, which, finding a place for localization and reproduction upon the free surface of the wound, act as new foci for a return of the disease. This manner of reproduction of the disease has recently received considerable attention, and has been called traumatic dissemination.

I have already alluded to the fact that even benign tumors sometimes manifest evidences of malignancy, and not infrequently, under certain conditions, they become malignant. The important question that presents itself to the surgeon is: *Are these tumors primarily benign, or are they malignant from the beginning and falsely diagnosticated as benign?* Virchow beautifully exemplifies this part of our discourse by alluding to the possibility of making an erroneous diagnosis by making only a partial microscopical examination of specimens which have been removed by operation. A surgeon, for instance, removes a tumor and sends it to a microscopist for examination. One section of the tumor is examined, and nothing but connective tissue is found, and consequently the tumor is pronounced a fibroma. The operation has been thorough, and yet the tumor returns. Examination of the second specimen shows the typical appearance of carcinoma. What are we to conclude? Did the fibroma undergo transformation into a carcinoma? Or, is it not more probable that the portion of tumor examined contained only fibrous tissue, while other portions contained a structure which, if examined, would have led to a correct diagnosis? This illustration is suggestive, and should teach us that, while we rely almost exclusively upon the microscope for the purpose of making an accurate anatomical diagnosis, to prevent mistakes it is necessary to make a thorough examination in doubtful cases by examining sections taken from different parts of the tumor. Eliminating mistakes of this kind, a certain class of tumors still remain which may be called doubtful. This is especially true of a

number of compound tumors which contain myxomatous tissue as one of their component parts. Again, numerous instances from authentic sources are on record where benign tumors, after a long period of stationary existence, assumed a malignant type. No better argument could be advanced in favor of the determining influences of the adjacent tissues in limiting or favoring tumor-growth than the transformation of a benign into a malignant tumor. The clinical history of nearly all such cases points to the existence of pathological changes in the vicinity of the tumor, which, by diminishing physiological resistance, have determined malignancy by creating a condition which makes it possible for the cells to infiltrate the surrounding tissues still further deprived of their physiological resistance. We have already learned that transplantation of morbid tissue into a healthy surrounding will fail to produce a tumor, because the physiological resistance will starve the transplanted tissue. A patient may harbor the matrix of a sarcoma or carcinoma for an indefinite period of time, and perhaps never suffer from the disease, because the physiological resistance has been adequate to prevent tissue-proliferation from the embryonal cells. So in a benign tumor, with tissue-elements closely resembling some malignant forms, in case a gradual loss of physiological resistance takes place, the cells no longer remain fixed, but permeate the tissue, and, by establishing independent centres of growth, impart to the tumor the type of malignancy. A combination of causes, which I have mentioned as elements in causing diminution of the physiological resistance when oc-

currence in the immediate vicinity of a benign tumor, must be looked upon as the direct causes of the transition of a benign into a malignant tumor.

We will now briefly consider the process of metastasis. By this I mean the formation of secondary tumors at some distance from the primary depot. I have already informed you that secondary multiplicity of tumors speaks in favor of their malignant character. A benign tumor seldom gives rise to metastasis. A case has recently been reported by Virchow where a benign colloid struma gave rise to multiple deposits in the lungs by perforation of a vein, entrance of tumor tissue, and dissemination by embolism of the pulmonary artery. The question naturally arises: *Through what channels do the tumor cells reach distant organs?* For a long time it has been known that the lymphatic vessels act as mediums of communication between the primary and secondary tumors. Experiments have proved that granular pigment material injected into the subcutaneous connective tissue is deposited in distant organs in the direction of the lymphatic current. This fact would tend to prove that the minute particles of pigment material reach the lymphatic vessels directly through the connective-tissue spaces, or that they are taken up by the colorless corpuscles, which convey them into these vessels and become arrested in their course in some of the proximal lymphatic glands, where liberation of the coloring material takes place. In metastasis tumor dissemination takes place by transportation of the tumor cells. Pathological anatomy furnishes strong proof that in some way the lymphatic vessels have a direct connection with the subcutaneous connective tissue and the

serous membranes, so that when an epithelioma comes in direct contact with these structures metastasis takes place in the course of the lymphatic vessels. Dissemination along the lymphatic channels must necessarily also take place, when during the growth of a carcinoma the walls of the vessels are destroyed, and thus a direct communication is established between the tumor and the nearest proximal lymphatic gland. You have had abundant opportunity to observe in the college clinic cases, where a primary carcinoma of the female breast leads to an uninterrupted chain of secondary deposits from the margin of the breast to the apex of the axillary space. Usually dissemination of carcinoma takes place in the direction of the lymphatic circulation, the first metastatic tumor occurring in the nearest lymphatic gland by a mechanical arrest of a tumor cell which had gained entrance into the lymphatic vessel, and its further transit arrested by the lymphatic gland acting as a first filter. Successive infection takes place from one gland to another until finally the last proximal gland, the last filter, is passed, when general dissemination takes place through the pulmonary and systemic circulation. In this form of metastasis the lymphatic glands act as barriers protecting the organism against general diffuse metastasis. In exceptional cases a carcinoma gives rise to diffuse metastasis in a more direct manner by perforation of a vein-wall leading to numerous distant foci by neoplastic emboli. The primary development of sarcoma is so intimately associated with the walls of the blood-vessels that we should naturally expect diffusion to take place, as a rule, along these channels by perforation of the vessel-

wall and diffuse systemic metastasis. This is what we observe in practice: seldom implication of the lymphatic system, but early extensive local diffusion through connective-tissue spaces and frequent general dissemination through the medium of the venous system. The manner of metastasis of sarcoma imparts to this class of tumors a greater malignancy as compared with carcinoma, where the lymphatic glands are interposed between the primary tumor and the general circulation.

In conclusion, I will again call your attention to the two essential conditions, one of which must precede and the other attend tumor-growth, and reiterate what I have said, viz., (1) that the essential condition is the presence of an embryonal tissue remnant, and that such a matrix can only proliferate tissue when the adjacent tissues have suffered; (2) impairment or suspension of physiological resistance.

